AMENDMENTS TO THE SPECIFICATION

Please insert the following on page 1, before FIELD OF INVENTION:

This a Continuation Application of U.S. Patent Application Serial No. 10/054,853, filed January 25, 2002, and claims priority from Provisional Application Serial No. 60/270,914, filed February 26, 2001.

Please amend the paragraph on page 1, line 4, to line 11, as follows:

The present invention relates to a ready-to-use absorbable composition for tissue gluing, tissue sealing and ~~haemostasis~~ hemostasis consisting essentially of a carrier coated with solidly fixed human components of fibrin glue: human fibrinogen and human thrombin. This fixed combination can be applied directly to e.g. a wound surface. Upon contact with blood, body fluids or physiological saline, the mechanism of this system mimics the final stage of the coagulation cascade, in which thrombin ~~catalyses~~ catalyzes the conversion of fibrinogen to fibrin and the activation of factor XIII to give XIIIa. ~~Faktor~~ Factor XIIIa, once formed, ~~stabilises~~ stabilizes the fibrin clot by covalent cross-linking.

Please amend the paragraph on page 1, line 13, to line 17, as follows:

Like a two-component adhesive, wound surface and carrier are glued together by ~~polymerisation~~ polymerization. During this process, which lasts approximately 3 to 5 minutes, the composition of the invention is preferably pressed onto the wound area. The components of the composition of the invention are degraded enzymatically in about 4 - 6 months after application.

Please amend the paragraph on page 1, line 21, to line 29, as follows:

Commercial fibrin glues, that mimic the last step of the coagulation cascade, consist of a highly concentrated fibrinogen solution to be mixed with a thrombin solution before application to the surgical wound exist. These mixtures contain a fibrinolysis inhibitor, e.g. aprotinin or ε-aminocaproicacid, to prevent premature dissolution of the fibrin clot by the fibrinolytic enzyme plasmin. These two-component fibrin glues are valuable in various surgical procedures but may

be washed away before ~~haemostasis~~ hemostasis is achieved if the bleeding is heavy. The two-component fibrin glues furthermore need some preparatory steps including thawing or dissolution. Thus, they are rather impractical and cumbersome to work with and experience is needed for successful use of these fibrin glues.

Please amend the paragraph on page 1, line 31, to line 34, as follows:

During the last decade numerous fibrin sealants became the methods of choice in surgery in a number of indications. However, in the majority of trials with fibrin glues a collagen fleece was additionally used to improve ~~haemostatic~~ hemostatic and adhesive features, indicating their disadvantages and their restrained use by the surgeons.

Please amend the paragraph on page 2, line 1, to line 14, as follows:

Collagen has been used as a ~~haemostatic~~ hemostatic agent since the late sixties. Collagen is the most frequent structural protein in all mammalians. The monomeric protein of approximately 300 kDa (tropocollagen) is covalently crosslinked at specific sites. The mature protein is therefore insoluble and forms characteristic fibrils with high tensile strength. Numerous sub-classes of collagen have been described, the most common of which is collagen type I, the main collagen type in skin, tendons, bones and cornea. Collagen is a fibrous protein consisting of a triple helix with a length of approximately 290 nm. Five of these triple helices (tropocollagen molecules) are staggered to form a microfibril with a diameter of approximately 3.6 nm. These microfibrils have polar and non-polar segments that are readily accessible for specific inter- and intrafibrillar interactions. Microfibrils are packed into a tetragonal lattice to form subfibrils with a diameter of about 30 nm. These subfibrils are then assembled into the collagen fibril, the basic unit of connective tissue, which has a diameter of several hundred nm and is therefore visible in the light microscope as a thin line.

Please amend the paragraph on page 2, line 16, to line 23, as follows:

Collagen may be used as a material for sealing wounds, possibly with a coating comprising a fibrin glue. Fibrin glues, i.e. the combination of fibrinogen, thrombin and aprotinin, have successfully been used therapeutically for many years for gluing tissues and nerves and for sealing surfaces when there is minor bleeding. One drawback of the fibrin glues has been that in case of major bleeding the glue is usually washed away before sufficient ~~polymerisation~~ polymerization of fibrin has occurred. To overcome this problem surgeons have begun applying manually liquid fibrin glues to absorbable carriers such as collagen fleece.

Please amend the paragraph on page 3, line 11, to line 16, as follows:

TachoComb® has been sold since the early 1990s by Nycomed Pharma and has been used in clinical trials in Europe in more than 2500 patients. The product has furthermore been used in more than 700 patients in the Japanese clinical ~~programme~~ program in a large variety of indications such as liver and lung resections, surgery of the biliary tract, splenic, renal and pancreatic surgery, ENT surgery, gynaecological surgery, and vascular surgery. TachoComb® was found to be effective and safe.

Please amend the paragraph on page 6, line 1, to line 4, to line 5 as follows:

In a presently preferred embodiment, the collagen carrier is produced as described in DK PA 2001 00135. The physical properties of three examples of collagen carriers are provided in the table below:

Example	I	II	III
pH value	~~5,3~~ 5.3	~~5,1~~ 5.1	~~5,4~~ 5.4
Lactic acid content	~~2,3%~~ 2.3%	~~2,8%~~ 2.8%	2%
Ammonium content	~~0,1%~~ 0.1%	~~0,2%~~ 0.2%	~~0,1%~~ 0.1%
Soluble protein content	~~0,04%~~ 0.04%	~~0,05%~~ 0.05%	~~0,08%~~ 0.08%

Sulphate ashes content	~~0,3%~~ 0.3%	~~0,3%~~ 0.3%	~~0,3%~~ 0.3%
Microbiological purity (CFU/g)	<12-345	<18-124	<11-33
Collagen content related to dry mass	95%	95%	98%
Water content	14%	15%	16%
Elasticity modul	~~10,4-42,1 N/cm~~ 10.4-42.1 N/cm	15-50 N/cm	~~12,3-41,0 N/cm~~ 12.3-41.0 N/cm
Pore size (diameter; mean value)	~~2,9mm~~ 2.9mm	~~2,1mm~~ 2.1mm	~~2,9mm~~ 2.9mm
Density	~~2,9-5,3mg/cm^3~~ 2.9-5.3mg/cm^3	~~2,9-5,9mg/cm^3~~ 2.9-5.9mg/cm^3	~~2,4-5,0mg/cm^3~~ 2.4-5.0mg/cm^3

Please amend the paragraph on page 6, line 7, to page 7, line 3, as follows:

Even distribution of the suspensions is carried out either using a drip-on-device as disclosed in US patent nos. 5,942,278 and 6,177,126 or an applicator comprising at least one jet may be used for applying the suspension to the carrier. The jet applicator is forcing the suspension through the jet while the carrier and the jet are moved relatively to ~~eachother~~ each other. The applicator may comprise or be arranged near a conveyor belt, a stirring unit connected to a pump or a system of pumps or another supplying equipment, and a jet or a system of jets which moves transversely, e.g. at right angles to the conveyor belt. Depending on the specific characteristics of the media, the jet or the system of jets may have various shapes and sizes. The jet or the system of jets may be connected to the supplying equipment via tubes. The supplying equipment may promote the coating medium from the stirring unit to the jet systems. During the coating process the jet system may move across the carrier. In its waiting position it may hold on one side of the conveyor belt. The coating process may be initiated by a light barrier sensing the presence of a carrier on the conveyor belt, and may likewise be stopped by a light barrier signal. Such an

applicator confers a relatively small dead volume, and it is easy to handle, including easy to clean. Furthermore, it confers the possibility to interrupt the coating process at any time, it is applicable in a relatively broad range of viscosities, and it confers a homogenous coating.

Please amend the paragraph on page 7, line 17, to line 22, as follows:

By the term "consisting essentially of" is meant that the three components are all essential and necessary for the invention. However, inessential additives such as calcium ions and a ~~colouring~~ coloring marker such as riboflavin can also be present in the composition. The composition may further comprise other useful ingredients such as one or more pharmaceutical active substances which may e.g. be selected from the group consisting of antibiotic, such as antibacterial or antimycotic, and antineoplastic agents.

Please amend the paragraph on page 8, line 13, to line 22, as follows:

First of all, TachoComb H has been developed as a follow-up product of TachoComb® with e.g. the bovine thrombin being replaced by human thrombin. Clinical experience with TachoComb H has been performed with regard to a number of therapeutic confirmatory (phase IIIa) clinical trials within the indications ~~haemostasis~~ hemostasis, tissue gluing and tissue sealing. The yet unpublished results gained in these studies confirmed the efficacy and safety of TachoComb H in the control of blood and air leakage, thus serving as an adjuvant therapy to suturing in ~~haemostasis~~ hemostasis, tissue gluing and tissue sealing during surgery. In particular, the efficacy of TachoComb H in achieving local ~~haemostasis~~ hemostasis, expressed as a significant reduction in ~~time-to-haemostasis~~ time-to-hemostasis compared to controls, was convincingly shown in vascular and liver surgery alike.

Please amend the paragraph on page 8, line 33, to page 9, line 3, as follows:

The present inventors devised new experiments in order to test this hypothesis that aprotinin was necessary. The *in vitro* experiments showed the antifibrinolytic protection of aprotinin in the clot and that TachoComb® without aprotinin (TachoComb S) was not dissolved within a very short

time. Therefore stressful animal models were designed and TachoComb S was compared to TachoComb H to prove similar efficacy. In all models TachoComb H or S, respectively, was used as only means of ~~haemostasis~~ hemostasis.

Please amend the paragraph on page 9, line 17, to line 22, as follows:

It can be concluded that the preclinical program designed to evaluate the overall necessity of aprotinin as a component of TachoComb H has proven similar efficacy of TachoComb H and TachoComb S. Both products have been used successfully as only means of ~~haemostasis~~ hemostasis, tissue gluing and tissue sealing under all experimental conditions. In the course of animal experiments, there were no undesirable tissue reactions. Consequently, aprotinin has been eliminated from the composition of the invention.

Please amend the paragraph on page 9, line 24, to line 30, as follows:

The composition of the invention is expected clinically to exert the same ~~haemostatic~~ hemostatic, tissue gluing and tissue sealing properties as its predecessors and to have the same or an even more satisfactory safety profile. The absence of aprotinin which is presently only available from bovine sources adds safety against hypersensitivity reactions. In this regard it should be noted that antibodies against aprotinin occurred in three Japanese studies. No such immunological response is anticipated with a composition without aprotinin.

Please amend the paragraph on page 10, line 11, to line 12, as follows:

and does not comprise any antfibronolytic agent such as aprotinin, ε-aminocaproic acid, or α2-antiplasmin,

Please amend the paragraph on page 10, line 14, to line 16, as follows:

the solid fibrinogen and solid thrombin being fixed to the carrier in a manner so that the abrasion is less than 1.0 mg/cm^2 when a sample of the coated material is shaken on a Vibrofix shaker at a ~~frequence~~ frequency of about 1000 rpm for 2 minutes and

Please amend the paragraph on page 10, line 18, to line 21, as follows:

if the coated carrier material is inserted into ~~an~~ endoscopic equipment and thereafter removed, the material is substantially unchanged and has cast ~~of~~ coating material less than 20% as an indication of the flexibility of the carrier and the solid adhesion of the solid fibrinogen and solid thrombin, and

Please amend the paragraph on page 10, line 23, to line 27, as follows:

~~said~~ the material being substantially air tight and liquid tight and having an elasticity factor of at least 1.25 as determined by a test comprising fixation of the coated carrier to a Latex sheet, expansion of the Latex by pressure three times and at the third time measuring the area of the coated carrier at the highest point of Latex sheet expansion and comparing the expanded area of the coated carrier with the starting area of the coated area.

Please amend the paragraph on page 11, line 2,as follows:

No problems with the ~~haemostatic~~ hemostatic running off or being rinsed off the target area

Please amend the paragraph on page 11, line 6, as follows:

Effective ~~haemostasis~~ hemostasis and tissue sealing within 3-5 minutes

Please amend the paragraph on page 11, line 7, as follows:

~~Favourable~~ Favorable safety profile, i.e. no bovine components

Please amend the paragraph on page 11, line 27, to page 12, line 2, as follows:

The ~~polymerisation~~ polymerization process produces a strong adhesion between wound surface and carrier patch. During the time required for gluing, i.e. 3 to 5 minutes, the composition of the invention should preferably be pressed gently onto the wound surface. The carrier patch provides mechanical support that allows tamponage of the wound. The patch keeps the coagulation components in place when wounds are bleeding profusely and prevents potential re-bleeding. The

mechanism of action involves the conversion by thrombin of fibrinogen into fibrin by splitting off peptides. Fibrin monomers ~~polymerise~~ polymerize spontaneously into fibrin strands forming a viscous and elastic clot, which glues the carrier patch to the wound surface. The fibrin matrix subsequently serves as scaffolding for fibrinoblast migration (Fig. 8).

Please amend the paragraph on page 12, line 4, to line 11, as follows:

Like a two-component adhesive, wound surface and carrier are glued together by ~~polymerisation~~ polymerization. The mechanical stability of the carrier patch adds a tamponade effect to the ~~haemostatic~~ hemostatic effect of fibrin clotting. Further, the active substances are only present on the carrier surface facing the wounded area and by virtue of the tamponade effect and the gentle pressure they do not diffuse through the carrier. Consequently, and in contrast to the situation when using most fibrin glues, there is no adhesion between the wounded area covered with the composition of the invention and other organs or parts thereof when the composition of the invention has been used.

Please amend the paragraph on page 12, line 23, to line 32, as follows:

The composition of the invention is useful for ~~haemostasis~~ hemostasis, tissue gluing and tissue sealing, in particular in surgical intervention in the gastrointestinal system, such as the ~~oesophagus~~ esophagus, stomach, small intestine, large intestine, rectum, on parenchymal organs, such as liver, spleen, pancreas, kidneys, lungs, adrenal glands, thyroid and lymph nodes, cardiovascular surgery, thoracic surgery including surgery on the trachea, bronchi or lungs, surgical interventions in the ear, nose and throat (ENT) area including dental surgery, gynaecological, urological, bone (e.g. spongiosa resection), and emergency surgery, neurological surgery, lymphatic, biliary, and cerebrospinal (CSF) fistulae, and air leakages during thoracic and pulmonal surgery. The present invention thus also relates to the use of the described compositions for the above purposes.

Please amend the paragraph on page 13, line 6, to line 8, as follows:

The product of the invention is to be applied when bleeding, or lymphatic, biliary, air or CSF leakage cannot be controlled with conventional methods or when these methods would yield ~~unfavourable~~ unfavorable results.

Please amend the paragraph on page 15, line 6, to line 8 as follows:

Fibrinogen raw-materials

~~Componen t~~ Component	% of total substance		
	~~Formulatio nA~~ Formulation A	~~Formulatio nB~~ Formulation B	~~Formulatio nC~~ Formulation C
Human fibrinogen	36-52	42-47	36-52
Human albumin	16-24	20-24	16-24
Total protein	52-76	62-71	52-76
Sodium chloride	8-14	0	8-14
tri Sodium citrate	2-4	1-3	2-4
Arginine (hydrochloride)	15-26	15-21	15-26
Glycine	0	6-9	1-2
Histidine	0	3-5	0
Sucrose	0	0	1-2
Residual moisture	<=2	2-4	~~<=1,5~~ <=1.5

Please amend the paragraph on page 16, line 14, to line 16, as follows:

Thrombin mixture:

- 100 ml ethanol (100% at -30°C)
- ~~12,27~~ 12.27 g human thrombin formulation B

Please amend the paragraph on page 21, line 22, to line 32, as follows:

TachoComb S is an off-white, coated, sponge-like patch. The patch of foamed dry collagen is used as carrier of the active, solid components. The size of the patch is 9.5 x 4.8 x 0.5 cm. The active side is ~~coloured~~ colored yellow. 1 cm^2 TachoComb S patch (thickness 0.5 cm) consists of:

Collagen of equine origin	2.1 mg
coated with:	
human fibrinogen	5.5 mg
human thrombin	2.0 I.U.
riboflavin (yellow ~~colour~~ color as marker of coated area)	16.5 μg

Please amend the paragraph on page 22, line 16, to line 18, as follows:

Composition of the incubation solutions:

All substances are diluted in buffer 1: 50mM Trometamol, 100mM NaCl, 2.5mM $CaCl_2$, 2mg/ml BSA (protease free), ~~0.5mg/ml Na-azid/ml)~~ 0.5mg/ml Na-azid/ml

Please amend the paragraph on page 22, line 23, as follows:

49μl buffer 1, pH ~~7,4~~ 7.4

Please amend the paragraph on page 22, line 24, as follows:

51μl plasminogen solution (conc. ~~4,9~~ 4.9μmolar Coachrom human plasminogen activity)

Please amend the paragraph on page 22, line 29, to line 30, as follows:

149μl buffer 1, pH ~~7,4~~ 7.4 51 μl plasminogen solution (conc. ~~4,9~~ 4.9μmolar Coachrom human plasminogen activity)

Please amend the paragraph on page 25, line 9, as follows:

Analytical balance (measurement precision ~~±0,5mg~~ ±0.5mg)

Please amend the paragraph on page 25, line 11, as follows:

Ruler with ~~millimetre~~ millimeter graduation

Please amend the paragraph on page 25, line 16, as follows:

The sample is placed in a balanced tube with ~~stopper. Then~~ stopper. Then it is shaken on the Vibrofix shaker (frequency: about 1000rpm) for 2min.

Please amend the paragraph on page 25, line 26, as follows:

Results

Carrier	Substance	Abrasion (mg/cm^2)
Opraskin®	lyoph. Collagen	~~2,1~~ 2.1
Willospon® forte (3mm)	lyoph. Collagen	~~1,2~~ 1.2
Willospon® Spezial (1mm)	Gelatine	~~2,1~~ 2.1
Ethisorb® Patch (ZVP609)	Polyglactin/dioxanon	~~14,3~~ 14.3
Tabotamp® NU Knit	oxidized cellulose	~~9,2~~ 9.2
Collagen sponge Nycomed	collagen, foamed	~~0,15~~ 0.15

Please amend the paragraph on page 26, line 3, to line 7, as follows:

The sample has to be cut out very cautiously. If it is cut out by using a pair of scissors a lot of the coating material will flake off because the layer in itself is rigid. Ethisorb® patch showed almost no connection with the coating material at all. When shaken a little bit, all of the coating peels off like a ~~„carpet“~~ "carpet".

Please amend the paragraph on page 26, line 16, as follows:

An area of ~~2x4,5cm²~~ 2x4.5cm^2 of each carrier was coated with TachoComb S coating suspension.

Please amend the paragraph on page 26, line 17, to line 18, as follows:

The amount of coating suspension corresponded to TachoComb specification (~~5,5mg~~ 5.5mg fibrinogen/cm^2). The samples were dried.

Please amend the paragraph on page 27, line 1, to line 2, as follows:

Silicone tubings and clamps, Latex gloves (Semper med), scalpel, ruler with ~~millimetre~~ millimeter graduation, scissors

Please amend the paragraph on page 27, line 6, to line 10, as follows:

The following equipment is connected air tight to the three outlets of the pressure buffering bottle via silicone tubings:

a) peristaltic ~~pumpe~~ pump

b) manometer

c) glass funnel/opening 2

Please amend the paragraph on page 27, line 22, to line 28, as follows:

Calculation:

„"Elasticity" factor = area of the carrier at third expansion
starting area of sample

Results

Carrier	Substance	Elasticity factor
Opraskin®	lyoph. collagen	~~1,78~~ 1.78
Willospon® forte (3mm)	lyoph. collagen	~~1,53~~ 1.53
Willospon® Spezial (1 mm)	gelatine	~~1,79~~ 1.79
Ethisorb® Patch (ZVP609)	Polyglactin/dioxanon	~~1,0~~ 1.0
Tabotamp® NU Knit	oxidized cellulose	~~1,15~~ 1.15

Collagen sponge Nycomed	collagen, foamed	~~1,55~~ 1.55

Please amend the paragraph on page 28, line 16, to line 17, as follows:

The amount of coating suspension corresponded to TachoComb specification (~~5,5mg~~ 5.5mg fibrinogen/cm^2). The samples were dried.

Please amend the paragraph on page 28, line 24, to line 25, as follows:

Endodock: Endoscopic tool designed for the use of TachoComb® in endoscopic surgery ~~(see Figure 7).Digital~~ (see Figure 7). Digital photo-equipment.

Please amend the paragraph on page 29, line 5, to line 6, as follows:

The sample has to be flattened manually to be able to wrap it around a guiding „"pin". Then the sample is inserted carefully into the steel tube of 10mm in diameter.

Please amend the paragraph on page 29, line 14, to line 23, as follows:

TachoComb S (coated equine collagen sponge/Nycomed) in endoscopic surgery is the most demanding application of the product. TachoComb S is inserted into an endoscopic equipment. The tube of this equipment is generally 10-13mm in diameter. To be inserted into the tube TachoComb S is flattened and then wrapped around a guiding „"pin" and then inserted carefully into the tube. Therefore the connection of the coating to the carrier and within itself has to be strong but the product has to stay flexible enough in dry condition to be bent and rolled up. When brought to the site of the surgery TachoComb S is carefully pulled out of the tube. Then it has to be unwrapped and placed to the wound surface. This often requires some adjustments. Therefore adhesion of the layer to the carrier should be strong enough to withstand this handling.

Please amend the paragraph on page 30, line 1, to line 6, as follows:

As Ethisorb® is a very rigid carrier the adhesion of the coating is very bad. Therefore coated Ethisorb® lost almost all of the coating in this investigation. Compared to coated collagen sponge

of Nycomed all the other investigated carriers have a flat surface to be coated. Therefore the coating lies like a „"flat carpet" on the carrier. This leads to a rather unflexible structure of the dry coated carriers. Bending or rolling up often breaks the coating in itself.

Please amend the paragraph on page 30, line 34, to page 31, line 2, as follows:

A wound of 1 x 1 cm and about 1 mm deep was made on the left lobe of liver of ~~anaesthetised~~ anesthetized rats in order to produce an oozing ~~haemorrhage~~ hemorrhage. The wound was sealed with a 1 x 1 cm piece of TachoComb S which was connected to a spring balance. The tension at which TachoComb S was torn off was measured.

Please amend the paragraph on page 31, line 5, to line 9, as follows:

A smooth level strongly bleeding wound was produced on the left kidney of ~~anaesthetised~~ anesthetized rats by cutting off about one quarter of its mass. The wound was sealed with TachoComb S test sheets. Tissue pressure was elevated by closing the venous drainage and pumping an isotonic citrate salt solution (pH 7.2) into the kidney. The pressure at which TachoComb S started to detach was measured.

Please amend the paragraph on page 32, line 21, to page 33, line 6, as follows:

The aim of this investigation was to compare the ~~haemostatic~~ hemostatic efficacy of TachoComb H (containing aprotinin) with TachoComb S (without aprotinin) in a canine model of spleen and liver lesions. Incision and puncture (0.5 cm depth) of the spleen were chosen to mimic oozing ~~haemorrhage~~ hemorrhage. Resection of the tip of the cranial liver lobe was performed to mimic a strongly bleeding surface wound (2 to 3 cm^2). A TachoComb H or TachoComb S patch was applied as the only means of ~~haemostasis~~ hemostasis to the wounds (same batch used for spleen and liver lesion in the same dog). Necropsy was done 48 hours after surgery as this is the period with the highest risk of re-bleeding in clinical practice.

Please amend the paragraph on page 33, line 8, to line 10, as follows:

Complete ~~haemostasis~~ hemostasis was achieved with both products. No case of secondary ~~haemorrhage~~ hemorrhage was observed at 48-hours necropsy neither at gross observation nor at histological examination.

Please amend the paragraph on page 33, line 12, to line 15, as follows:

Also histologically there were no differences between dogs applied TachoComb H or TachoComb S when evaluating splenic and hepatic lesions covered with the respective patches with regard to ~~haemostasis~~ hemostasis and healing of the wound. No case of secondary hemorrhage was observed after surgery.

Please amend the paragraph on page 34, line 3, to line 4, as follows:

Comparative ~~Haemostatic~~ Hemostatic, Wound Sealing Effect and Resistance of Absorbable TachoComb S and TachoComb H: Experimental Study in the Pig

Please amend the paragraph on page 34, line 7, to line 8, as follows:

The test was designed to assess the immediate efficacy and short term resistance of a ~~haemostatic~~ hemostatic fleece on a spleen lesion induced in the pig.

Please amend the paragraph on page 34, line 11, to line 12, as follows:

24 female pigs were used in the study. 2 groups of ~~haemostatic~~ hemostatic fleeces were randomly tested: TachoComb H with aprotinin and TachoComb S without aprotinin.

Please amend the paragraph on page 34, line 14, to line 15, as follows:

On the day of surgery the animal received a fleece directly obturating a ~~standardised~~ standardized 2 x 3 cm lesion surgically created on the ventral part of the spleen.

Please amend the paragraph on page 34, line 17, to line 19, as follows:

The immediate and ~~haemostatic~~ hemostatic effect of the fleece was estimated, by counting the number of blisters and measuring the time necessary to stop ~~haemorrhage~~ hemorrhage. The adherence of TachoComb H and S was noted.

Please amend the paragraph on page 34, line 21, to line 22, as follows:

After 72 hours, the short term ~~behaviour~~ behavior and resistance of both materials was investigated by increasing the intrasplenic pressure (clamping of the venous vessels).

Please amend the paragraph on page 34, line 32, to line 33, as follows:

No difference was detected between treatments at the time of spleen lesion surgery on the ~~haemostatic~~ hemostatic effect.

Please amend the paragraph on page 35, line 15, to line 16, as follows:

The immediate ~~haemostatic~~ hemostatic activity of 2 formulations of TachoComb, S and H, was investigated in ~~standardised~~ standardized spleen lesion model in 24 pigs.

Please amend the paragraph on page 35, line 30, to line 2, as follows:

TachoComb S or TachoComb H were used as only means of ~~haemostasis~~ hemostasis to seal strongly bleeding splenic lesions in pigs (surface lesion 2cm x 3cm, 3-5mm depth; n=12 per group). After 72 hours the intrasplenic pressure was increased by ligating the splenic vein(s). Thereafter intrasplenic pressure was additionally increased by injecting adrenaline. The pigs were observed for signs of rebleeding or occurrence of blood blisters under the patch. Histopathology of samples (lesion site sealed with TachoComb H and S) was performed after necropsy.

Please amend the paragraph on page 36, line 9, to line 11, as follows:

Comparative ~~Haemostatic~~ Hemostatic Wound Sealing Effect and Resistance of Absorbable TachoComb S and TachoComb H: Experimental Study in the Pig in a Model of Acute Pancreatitis

Please amend the paragraph on page 36, line 14, to line 15, as follows:

The test was designed to assess the immediate efficacy and short term resistance of a ~~haemostatic~~ hemostatic fleece on a spleen lesion induced in the pig in a model of acute pancreatitis.

Please amend the paragraph on page 36, line 18, to line 19, as follows:

20 female pigs were used in the study. 2 groups of ~~haemostatic~~ hemostatic fleeces were randomly tested: TachoComb H with aprotinin and TachoComb S without aprotinin.

Please amend the paragraph on page 36, line 21, to line 22, as follows:

On the day of surgery the animals received a fleece directly obturating a ~~standardised~~ standardized 2 x 3 cm lesion surgically created on the ventral part of the spleen.

Please amend the paragraph on page 36, line 24, to line 26, as follows:

The immediate ~~haemostatic~~ hemostatic effect of the fleece was evaluated, by counting the number of blisters and measuring the time necessary to stop ~~haemorrhage~~ hemorrhage. The adherence of TachoComb H and S was noted.

Please amend the paragraph on page 37, line 1, to line 3, as follows:

After 72 hours, the short term ~~behaviour~~ behavior and resistance to enzymic degradation of TachoComb H and S were investigated by increasing the intrasplenic pressure (clamping of the venous vessels and pharmacological means).

Please amend the paragraph on page 37, line 14, to line 16, as follows:

On the spleen, both materials behave similarly for immediate ~~haemostatic~~ hemostatic efficacy, adherence to the lesion and compliance to the parenchyma. Their efficacy was very impressive.

Please amend the paragraph on page 38, line 9, to line 15, as follows:

The ~~haemostatic~~ hemostatic efficacy of TachoComb S and TachoComb H was investigated in a ~~standardised~~ standardized spleen lesion model (surface lesion 2cm x 3cm, ca 3mm depth; n=10/group) in pigs with acute pancreatitis induced by retrograde injection of bile in the Wirsung's duct and subsequent ligation of the pancreatic duct. Small pieces of TachoComb H and S were also applied on the pancreas at the site of pancreatic duct ligation. At 72 hours after surgery intrasplenic pressure was increased by ligating the splenic vein and i.v. adrenaline injection.

Please amend the paragraph on page 38, line 17, to line 26, as follows:

On the spleen TachoComb S and TachoComb H behaved similarly with regard to immediate ~~haemostatic~~ hemostatic efficacy, adherence to the lesion and resistance to increased intrasplenic pressure despite marked increase of pancreatic enzyme levels (20-100 fold increase of amylase and lipase in blood and 10-100 fold increase of pancreatic enzymes in peritoneal fluid as compared to basal levels). Histopathologic findings indicated no significant difference in the degradation of TachoComb S and TachoComb H. No specific cellular pattern was observed on the spleen. Even on pancreatic samples following close contact of TachoComb H and S with high concentrations of pancreatic enzymes, the adherence of TachoComb H and S and histopathology did not reveal any major differences.

Please amend the paragraph on page 39, line 9, to line 19, as follows:

Two out of three lesions per hemisphere were treated with TachoComb H or TachoComb S respectively and one lesion per hemisphere was left empty as control. After sealing the lesions with TachoComb H or S bleeding time was measured under high magnification with continuous

low flow irrigation with saline. After ~~haemostasis~~ hemostasis was achieved in all lesions, arterial hypertension was induced by i.v. adrenaline injection (0.01mg/kg adrenaline), thus increasing mean arterial pressure (MAP) to at least 120mmHg. During this procedure observation for rebleeding continued. After lowering the MAP to normal values again the skin was closed. Time to necropsy was 3 and 7 days (n=5 rabbits each). In three animals magnetic resonance imaging was performed before necropsy on day 3. At necropsy a gross observation of the lesion sites was performed and samples for histopathology were taken.

Please amend the paragraph on page 40, line 6, to line 8, as follows:

Fluid fibrin sealants are used on a large scale for ~~haemostasis~~ hemostasis in neurosurgery. There exists no comprehensive published data on the brain tissue reaction to TachoComb® and the use of antifibrinolytic agents (i.e. aprotinin) is still controversial.

Please amend the paragraph on page 41, line 5, to line 8, as follows:

Under normal coagulation (BTR animals), ~~haemostasis~~ hemostasis with TCH and TCS was significantly faster ($p<0.001$) than with no hemostatic agent. It was demonstrated that there is no difference between the bleeding times of both products ($p=0.294$), but that these times are consistently shorter than those of the blank lesions ($p<0.001$).

Please amend the paragraph on page 41, line 34, to line 34, as follows:

As compared to the literature, TachoComb H and S establish much faster ~~haemostasis~~ hemostasis than ~~oxidised~~ oxidized cellulose and collagen fleece.